REMARKS

Amendments to the Specification

Applicants replaced the title with a new title, HUMAN K^+ ION EAG CHANNELS." Support for this amendment can be found, for example, on page 3, line 9 of the specification.

Applicants have amended the specification by adding sequence identifying numbers as required under 37 C.F.R. §§ 1.821–1.825 (that is, of the SEQ ID NOS found, for example, on page 9, line 29; page 11, line 17; page 30, lines 18–19 and lines 21–22; page 33, lines 16–17; page 36, lines 26–27; page 37, lines 19–21; and page 39, lines 10–12). Support for these amendments can be found in the Sequence Listing as filed and throughout the specification.

Applicants further amended the specification as follows. For example, on page 9, lines 29-30, applicants rearranged the phrase "were designed" in the sentence. On page 30, line 19, applicants replaced the word "sequences" with "sequence." On page 36, line 24 and page 37, line 2, applicants corrected the spelling of "chord." On page 37, line 19, applicants replaced the sequence "5'-CGCATGAACTACTGAAGACG" with the sequence "5'-CGCATGAACTACCTGAAGACG," to correct an obvious typographical error. Support for this amendment can be found on page 36, line 26 and in the Sequencing Listing as filed (e.g., SEQ ID NO:10; nucleotides #898–918 of Figure 10, SEQ ID NO:1 and SEQ ID NO:2; and nucleotides #861–882 of SEQ ID NO:13 and SEQ ID NO:14).

Amendments to the Claims

Applicants have canceled claims 2, 11–13, 16–31 and 33 without prejudice.

Applicants have amended claim 1(c) to recite stringent hybridization conditions "at 4XSSC at 65°C or at 4XSSC at 42°C in 50% formamide" immediately after "(b)". Support for the amendment can be found, for example, on page 4, lines 10–12.

Applicants have amended claims 3–6, 14, 15 and 32 to remove dependency from canceled claim 2.

Applicants have amended claim 8 to recite "cell" following "host." Support for this amendment may be found, for example, on page 14, line 16 to page 15, line 18.

Applicants have amended claim 9 to recite "host cell" instead of "host." Support for this amendment may be found, for example, on page 14, lines 16 to page 15, line 18.

Applicants have further amended claim 14 to improve its form by canceling "and/or the" and substituting therefor "an." Applicants have further amended claim 14 by adding "or, optionally, in further combination with any one of the nucleic acid molecule, the vector, the polypeptide or the antibody," immediately before "wherein." Support for this amendment can be found, e.g., in claim 14 as originally filed. Applicants have also canceled the recitation of "and/or diluent and/or excipient." It should be understood that the composition of claim 14 as amended can include a diluent or an excipient.

Applicants have further amended claims 15 and 32 by canceling "and/or" and substituting therefor "or" to improve their form. Applicants have further amended claim 32 to remove dependency from canceled claims.

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Applicants have added claims 34–44. The added claims are directed to embodiments recited in claims 1, 5, 6, 8, 10, 14, 15 and 32. Support for the added claims may be found throughout the specification and originally filed claims 1, 5, 6, 8, 10, 14, 15 and 32. For example, support for claim 34 may be found on page 28, lines 7–10. Support for claims 35–37 may be found, e.g., on page 2, lines 16–26. Support for claim 38 may be found, e.g., on page 13, lines 7–9. Support for claim 39 may be found, e.g., on page 13, line 10 to page 14, line 15. Support for claim 40 may be found, e.g., on page 14, line 16 to page 15, line 18. Support for claim 41 may be found, e.g. on page 15, lines 19–21. Support for claim 42 may be found, e.g., on page 16, lines 19–27. Support for claim 43 may be found, e.g., on page 20, lines 15–26. Support for claim 44 may be found, e.g., on page 28, lines 7–21.

No new matter has been added. Claims 1, 3–10, 14, 15, 32 and 34–44 are pending. Applicants reserve the right to pursue the removed subject matter in applications claiming benefit herefrom.

The Restriction Requirement

The Examiner has maintained her restriction with regard to Group II. Accordingly applicants reaffirm their election of Group I (claims 1–10, 14, 15, and 32) for substantive examination. As discussed above, applicants have canceled claim 2, the remaining claims not in Group I and have added claims 34–44. Claim 34 depends from claim 32 (Group I claim). Further, as discussed above, claims 34–44 are directed to embodiments recited in claims 1, 5, 6, 8, 10, 14, 15, and 32 (Group I claims). Therefore, applicants request that the Examiner consider added claims 34–44 with the claims of Group I.

The Informalities

The Examiner has objected to the former title of the invention for not clearly describing the invention to which the claims are directed. As discussed above, applicants have amended the title to recite "human K^+ EAG ion channels," thereby obviating the objection.

The Examiner has stated that the application is not fully compliant with sequence rules as set forth in 37 C.F.R. §§ 1.821–1.825, in particular 37 C.F.R. § 1.821(c). Applicants file herewith a Substitute Sequence Listing to comply with the sequence rules as set forth. As discussed above, applicants have amended the specification to add sequence identification numbers corresponding to the sequences in the Sequence Listing as filed, thereby overcoming this objection.

The Objections

The Examiner has objected to claims 1, 8, 14, 15 and 32 because she states that they recite or encompass non-elected inventions. Applicants traverse the objection with regard to claims 1, 8, 14 and 15. Applicants also traverse in part the objection to claim 32.

In the June 30, 2001 Office Action ("Office Action"), the Examiner restricted the claims into eleven groups, including Group I[2] (nucleic acids, etc.) and Group III (polypeptides, etc). The Examiner also requested that applicants elect one sequence from one of the following two groups: Group A (SEQ ID NOS:3 or 4, which are polypeptide sequences) or Group B (SEQ ID NOS:13 or 14, which are nucleic acid sequences). See page

[2] Group I contains former claims 1–10, 14, 15 and 32.

3, lines 3–7 of the Office Action. Applicants selected Group I with traverse and elected SEQ ID NO: 14. See page 6 of the November 30, 2001 Response ("Response").

Now, the Examiner has objected to claims 1, 8, 14, 15 and 32 (Group I claims) because she states that they recite or encompass non-elected inventions. Applicants have amended claim 32 by removing dependency from non-Group I claims. However, former and amended claims 1, 8, 14, 15 and amended claim 32 do not depend from non-Group I claims. In the event that the Examiner is objecting to amended claims 1, 8, 14, 15 and 32 on the basis that they recite SEQ ID NOS:3, 4 and 13, applicants believe that those objections are improper for the reasons discussed below.

Former claim 1(a) recites, inter alia, nucleic acid sequences encoding the polypeptide having the amino acid sequence SEQ ID NO:3 or SEQ ID NO:4. Former claim 1(b) recites, inter alia, the nucleic acid sequences SEQ ID NO:13 or SEQ ID NO:14. Former claim 1(c) recites nucleic acid sequences that hybridize to the nucleic acid molecules of (a) and (b). Former claim 1(d) recites nucleic acid sequences that are degenerate to the sequence of the nucleic acid molecules of (c). Thus, former claims 1(a) and (b) recite SEQ ID NOS: 3, 4, 13 and 14. As amended, claim 1(a) and (b) continue to recite SEQ ID NOS: 3, 4, 13 and 14. Amended claims 8, 14, 15 and 32 depend from claims 1 and/or 2.

SEQ ID NO:14 is a nucleic acid sequence encoding an EAG polypeptide. SEQ ID NO:13 is a nucleic acid sequence that is a splice variant of SEQ ID NO:14. SEQ ID NO: 4 is a polypeptide that can be encoded by SEQ ID NO:14. SEQ ID NO:3 is a polypeptide that can be encoded by SEQ ID NO:13. Thus, SEQ ID NOS: 13 and 14 of claim

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1(b) are species of the nucleic acid sequences encoded by the polypeptide having the amino acid sequences of SEQ ID NOS: 3 and 4, respectively, in claim 1(a).

In her Office Action, the Examiner identified two "sets" of "patentably distinct inventions"—Group A and Group B sequences. See page 6, lines 13–16 of the Office Action. The Examiner stated that Group A are polypeptide sequences and Group B are nucleic acid sequences. See page 6, line 18 of the Office Action. Applicants elected one nucleic acid sequence in Group B—that is, SEQ ID NO:14. In making the their election, applicants understood that the restriction of the prosecution to the species would only be maintained if an generic claim is finally held not to be allowable. MPEP 809.02(a). Thus, applicants believed that prosecution on the merits relating to the generas of nucleic acid molecules in claim 1(a), which recite SEQ ID NOS: 3 and 4 and the nucleic acid molecules in claim 1(b), which recite SEQ ID NOS:13 and 14 would proceed unless a nucleic acid molecule comprising SEQ ID NO:14 was found not to be allowable.

If the Examiner is now asserting that nucleic acid molecules comprising the sequence SEQ ID NO:13 are restricted from nucleic acid molecules comprising the sequence SEQ ID NO:14, then the applicants believe such restriction is improper. As discussed above, SEQ ID NO:13 is a splice variant of SEQ ID NO:14. In fact, SEQ ID NO:13 (2886 bp) is identical to SEQ ID NO:14 (2967 bp) except for the absence of 81 nucleotides. There is absolutely no undue burden to conduct a search encompassing SEQ ID NO:13 and SEQ ID NO:14 together. Accordingly, the Examiner should expand her search to encompass the nucleic acid molecule comprising the sequence SEQ ID NO:13 and the generas of nucleic acid molecules in claim 1(a) if allowable as discussed above. If the Examiner maintains her

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objection, applicants request that the Examiner contact the undersigned for a telephonic interview.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected former claims 1–10, 14, 15 and 32 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not provide enablement for making or using all of the possible polypeptides or polynucleotides as claimed. The Examiner states that undue experimentation would be required to make all possible proteins expressed by the claims and to determine a structure–function relationship for each possible polynucleotide or polypeptide. In particular, the Examiner contends that the breadth of the claims is too large because claim 1(c) recites no stringency conditions for the recited polynucleotide and reads on polynucleotides that bind under low-stringency conditions or no-stringency conditions. The Examiner states that the specification does not provide any guidance on how to produce all nucleotides that hybridize under low stringency conditions and still retain the functions of the claim polypeptides. Further, the Examiner alleged that the scope of former claims 1–10, 14, 15 and 32 is too broad because they lack the recitation of functional activity to narrow their scope.

Applicants have amended claim 1(c) to recite specific high stringency hybridization conditions. Further, contrary to the Examiner's assertion, claim 1 as originally filed and as amended in fact recites the phrase "a polypeptide having a function of human K^+ ion *eag* channel." Further, claim 2 has been canceled, thereby obviating the rejection. One of ordinary skill in the art could easily make and use the nucleic acid molecules of amended

claim 1 and claims 3–10, 14, 15 and 32 depending therefrom. Accordingly, amended claim 1 and claims depending therefrom are enabled by the specification as filed.

The Examiner has rejected former claims 3–10, 14, 15 and 32 as being too large in breadth in that they read on the primer sequence of former claim 2. Applicants believe that the rejection is improper. Applicants have the right to pursue a plurality of claims that are not duplicative. MPEP §706.03(k). A rejection of former claim 2 is improper for the same reason. However, as discussed above, applicants have canceled claim 2, thereby obviating the rejection.

The Examiner has rejected claim 2 for lacking enabling support in the specification that discloses how to make all the polynucleotides that would comprise the nucleic acid molecule recited in claim 2. As discussed above, applicants have canceled claim 2 thereby obviating the rejection.

The Examiner has rejected the composition of claim 15 for not being enabled by the specification for use in a "diagnosis." Specifically, the Examiner states undue experimentation would be required because that the specification lacks enabling discussion or working examples as to which disease related to the K^+ channel is disclosed in the specification and how one would practice the method of diagnosing a disease. The Examiner also contends that undue experimentation would be required to determine how to use the disclosed sequences to diagnose a condition because the state of the art is silent concerning the diseases related to this channel and the breadth of the claim, which embraces potentially many diseases. The Examiner states that undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope. Applicants traverse.

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The application as filed states that diagnostic compositions are useful in detecting the onset or progress of diseases related to the undesired expression or overexpression of the nucleic acid molecule of the invention (e.g., page 20, lines 18–20 of the specification as filed). The application states that the diseases are interrelated or caused by an increased or ongoing cellular proliferation (e.g., page 20, lines 20–21 of the specification as filed). The application more specifically teaches that methods of this invention can be used to diagnose cancer such as breast cancer, neurodegenerative diseases, or psoriasis (e.g., page 27, lines 1–8 of the specification as filed). Further, the application discloses that the quantitative and qualitative analyses of the expression level of human *eag* can be indicative of, e.g., cancer, psoriasis and neurodegenerative diseases (page 12, lines 26–31 of the specification).

The application teaches that the diagnostic composition comprises the nucleic acid molecule of the invention, the vector of invention, the polypeptide of the invention and/or the antibody of the invention (e.g., page 20, lines 15–17 of the specification as filed). The application states that suitable protocols for carrying out the method of the invention are well-known in the art and include, Northern blotting for the assessment of the level of mRNA or the analysis of tissue by microscopic techniques using antibodies that specifically recognize the polypeptide of the invention (e.g., page 27, lines 10–13). Further, the application exemplifies the use of techniques known in the art, such as RT-PCR, to evaluate the expression of the *EAG* of this invention in diseased or normal cells or tissues (e.g., page 31, lines 15–19; Figure 15; Example 2). Accordingly, one of ordinary skill in the art could diagnose a disease, for example, by determining the level of EAG nucleic acid and/or protein expression in a normal tissue and a tumor tissue, and compare the values obtained therefrom.

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Based on the teachings of the specification, one of ordinary skill in the art would know how to diagnose a disease according to this invention using the diagnostic compositions of the application and the methods of the application.

To further demonstrate this point, applicant submits herewith the Declaration of Dr. Luis Angel Pardo-Fernandez ("Pardo Declaration"). Dr. Pardo-Fernandez is an inventor of this application. Dr. Pardo-Fernandez and his colleagues performed studies using diagnostic compositions of this invention on normal and cancerous tissue according to the methods described in the specification. As discussed in paragraphs 9–17 of the Pardo Declaration, they measured the levels of *EAG* RNA expression in normal tissues or breast tissue from primary tumor biopsies using a diagnostic composition comprising nucleic acid molecules of this invention and real time PCR (RT-PCR). They demonstrated that *EAG* RNA is overexpressed in neoplastic mammary gland tissue, taken from mammary tumor biopsies, compared to normal mammary gland tissue or tumor-free tissue of breast cancer biopsy specimens. This data supports the use of diagnostic compositions of this application in the diagnosis of diseases.

Further, Dr. Pardo and colleagues used a diagnostic composition comprising an anti-EAG monoclonal antibody to detect EAG in a multitude of cancerous tissues by immunohistochemical techniques. As discussed in paragraphs 19–24 of the Pardo Declaration, using qualitative and quantitative analysis, they confirmed that the overexpression of EAG protein in cancerous tissue is strongly correlated to the occurrence of cancer. This data further supports the use of diagnostic compositions of this application in the diagnosis of diseases.

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Accordingly, the diagnostic compositions of this invention are enabled for the full scope of claim 15. Applicants request that the Examiner withdraw the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected former claims 1, 2, 8, 10 and 14, under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner states that claim 1 is indefinite because it is difficult to contemplate the nature of a degenerate sequence of a complement. As discussed above, applicants have amended claim 1(c) to recite high stringency conditions. One or ordinary skill in the art could easily contemplate the nucleic acid molecules of claim 1(d), which are degenerate to the nucleic acid sequences of claim 1(c).

The Examiner has stated that former claim 2 is indefinite because there is no antecedent basis for "the" nucleic acid. As discussed above, applicants have canceled claim 2, thereby obviating the rejection.

The Examiner has stated that former claim 8 is indefinite because it is not clear what type of organism is indicated by the word "host." Applicants have amended claim 8 to recite "host cell," thereby obviating the rejection.

The Examiner has stated that former claim 10 is indefinite because the specification does not teach how to recombinantly produce a polypeptide from the complementary nucleic acid of claim 1(c) or claim 2. As discussed above, applicants have amended claim 1(c) to recite specific hybridization conditions and have canceled claim 2. One of ordinary skill in the art could easily use known recombinant engineering techniques to

manipulate the claimed nucleic acid molecules of amended claim 1(c) to express a polypeptide, e.g., Sambrook, J., Fritsch, E.F., and Maniatis, T. (1989). Molecular Cloning: A Laboratory Manual. Second Edition., Plainview, New York: Cold Spring Harbor Laboratory Press. Claim 10 is not indefinite.

The Examiner has stated that former claim 14 is indefinite because there is no antecedent basis for "the" antibody. The applicants have amended claim 14 to recite "an" antibody to overcome the rejection. The Examiner has stated that claims 14, 15 and 32 are indefinite under 37 C.F.R. § 1.75, for reciting "and/or" and therefore being in improper dependent form. As described above, applicants have amended claims 14, 15 and 32 by replacing "and/or" with "or" to place them in proper dependent form, thereby obviating the rejection.

Rejections under 35 U.S.C. § 102(b)

The Examiner has rejected former claims 1 and 3–10, under 35 U.S.C. § 102(b), as being anticipated by Warmke *et al.*, Proc. Acad. Natl. Sci. U.S.A. 91: 3438–3442 (1994) ("Warmke"). Specifically, the Examiner states that Warmke discloses a K^+ channel that exhibits 45%–51.2% sequence homology to SEQ ID NO: 14. As discussed above, applicants have amended claim 1(c) to recite high stringency conditions. The nucleic acid sequences that hybridize at the high stringency conditions recited in claim 1(c) have sequence homologies to SEQ ID NO:14 that are greater than 51.2%. Accordingly, the nucleic acid molecules of amended claim 1 and claims depending therefrom have sequence homologies to SEQ ID NO: 14 that are greater than the Warmke sequence. Therefore, amended claims 1 and 3–10 are not anticipated by Warmke.

Conclusion

In view of the foregoing, applicants request allowance of pending claims 1, 3–10, 14, 15, 32 and 34–44. To expedite prosecution, applicants invite the Examiner to telephone the undersigned to discuss any matter that may be handled over the telephone.

Respectfully submitted,

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Appendix of Amendments

IN THE SPECIFICATION

On page 1, in the Title: [NOVEL] HUMAN K^+ ION EAG [CHANNEL FAMILY AND THERAPEUTIC APPLICATIONS THEREOF] CHANNELS

On page 9, line 22 to page 10, line 18:

Due to the prior art failures to clone human *eag* gene from brain libraries and the above recited uncertainties with immortalized cell lines, another source for a library was in need. The 400 bp fragment was therefore used to screen a normal human breast cDNA library. Due to the presence of *eag* is breast cancer cells, such a library was expected to comprise h*eag* clones. Surprisingly, however, after screening 2x 10^6 phages, no human-*eag* clones could be identified in said library. This rises the possibility that the channel is expressed only in tumor cells, and not in normal tissue. Specific oligonucleotides, namely 5'-CCAAACACACACACCAGC (SEQ ID NO: 5)[,] and 5'-CGTGGATGTTATCTTTTTGG (SEQ ID NO: 6), were designed to check for h*eag* fragments by PCR amplification directly from the above library [were designed], but no evidence for the presence of any *eag* clones in this library was found. In view of the above discussed prior art results, it came as a further surprise that the same primers detected h*eag* in a normal human brain cDNA library, that was therefore screened. First, the probe obtained from MCF7 cells was used to check 10^6 phages. This procedure allowed to isolate a 1.6 kbp fragment from human *eag*. This fragment was then used as a probe for the screening of $2x10^6$ phages from the same library. Several independent clones were isolated, but none of them was a full-length clone. Furthermore,

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only one clone contained the 5' end of the sequence, while two of them contained the 3' end and part of the 3' non-coding region. It is likely that the abundance of restriction sites in the nucleic acid sequence encoding the channel has induced this extensive fragmentation of the cDNA. For example, when EcoRI was used to extract the inserts of the library that was cloned in λ-gt10 phage at the EcoRI site, this conventional approach systematically failed to find the 5' end of the molecule (there is an EcoRI site at position 400 of the clone). The pooled positive clones were therefore screened again by PCR, trying to amplify the start codon, and only by this means was it possible to isolate one phage that contained this ATG. Two splice variants of h*eag* were cloned, both expressed in brain tissue. The [sequence] sequences obtained for h*eag* 1 and h*eag* 2 and their deduced amino acid [sequence] sequences are shown in Figures 10 and 11, and compared to other members of the family.

On page 11, lines 15–17:

The present invention also relates to a nucleic acid molecule specifically hybridizing to the nucleic acid molecule of the invention which comprises the sequence 5'-GGGAGGATGACCACATGGCT (SEQ ID NO: 7).

On page 30, lines 18–20:

Figure 10. Nucleotide sequence of human-*eag* cDNA (heag; SEQ ID NO: 1) from human brain compared to the rat sequence (reag; SEQ ID NO: 20) and bovine [sequences.] sequence (beag; SEQ ID NO: 19). Those positions showing a different nucleotide in any of the sequences are shaded.

On page 30, lines 21–23:

Figure 11. Amino acid sequences of both splice variants (heag1 (SEQ ID NO: 3) and heag2 (SEQ ID NO: 4)) obtained from human *eag* cDNA translation, compared to the corresponding bovine (beag1; SEQ ID NO: 21; beag2; SEQ ID NO: 22), mouse (meag; SEQ ID NO: 23) and rat (reag; SEQ ID NO: 24) sequences. The black boxes indicate a different residue in any of the sequences.

On page 33, lines 15–17:

The sequences of the oligonucleotides were the following:

5'-CAGAA(T,C)AA(T,C)GTGGC(A,C,T,G,)TGGCT (SEQ ID NO: 8)

5'-TCACT(G,A)AAGATCTATA(A,G)TC (SEQ ID NO: 9)

On page 36, line 24 to page 37, line 8:

500 ng total RNA from different tissues (or 5 ng polyA$^+$ RNA, for spinal [chord] cord) were reverse transcribed and amplified using a pair of oligonucleotides of the sequences 5'-CGCATGAACTACCTGAAGACG (SEQ ID NO: 10) (forward) and 5'-TCTGTGGATGGGGCGATGTTC (SEQ ID NO: 11) (reverse). The amplified DNA was analyzed by Southern blot using a specific human *eag* probes (a 1.5 kb EcoRI fragment from the core of the channel). Among the RNAs tested, only brain total RNA gave positive signals. RNAs from spinal [chord] cord, adrenal gland, skeletal muscle, heart trachea, liver, kidney and mammary gland were negative. The integrity of the RNA was checked using transferrin amplification. Using the same approach, the expression of h*eag* in several tumoral human cell lines was checked, in: MCF-7 (breast adenocarinoma), BT-474 (breast ductal

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carcinoma, from a solid tumor, EFM-19 (breast carcinoma, ductal type, from pleural fluid), COLO-824 (breast carcinoma, ductal type, from pleural fluid), SHSY5Y (neuroblastoma).

On page 37, lines 11–30:

Further, Southern blot of RT-PCR products of RNAs from different human tissues and 293 cells show that only in RNA from brain the two bands corresponding to h*eag* A and B could be amplified and identified. Transferrin receptor (TFR) signals are shown at the bottom (Fig. 15A). Furthermore, a Southern blot analysis of RT-PCR products of total RNAs from different human cell lines an mammary epithelial cells in primary culture (Epith. cells). TRF signals are shown at the bottom. RNAs from different cell lines (34) and commercial RNAs from human tissues (Clontech) were subjected to single-tube RT-PCR (35). Total RNA was used with the exception of spinal cord, where poly(A)$^+$ RNA was used (primer sequences were: forward: [5'-CGCATGAACTACTGAAGACG] 5'-CGCATGAACTACCTGAAGACG (SEQ ID NO: 10) and reverse: 5'-TCTGTGGATGGGGCGATGTTC (SEQ ID NO: 11). 5'-TCAGCCCAGCAGAAGCATTAT (SEQ ID NO: 17) and reverse: 5'-CTGGCAGCGTGTGAGAGC (SEQ ID NO: 18) were used to control RNA and PCR performance.). Specific primers for TFR were used to control RNA and PCR performance. These ODNs were designed according to the published TFR sequence (36), starting at exon 11 and spanning to exon 19 (37). This, together with the amplification of two h*eag* splice fragments and controls in the absence of reverse transcriptase, excludes a false positive due to genomic DNA contamination. 50 µl (h*eag*) or 15 µl (TFR) of PCR reactions were analyzed in 2% agarose gels. DNA was transferred to membranes and consecutively hybridized at

high stringency with [^{32}P]-dCTP labeled random primed probes consisting of a 980 bp h*eag* fragment and the TFR fragment amplified from brain RNA.

On page 39, lines 6–15:

It is assumed that expression of h*eag* in some tumor cells is not the consequence of their abnormal growth, but that this K^+ channel is necessary for their proliferation. Therefore, inhibition of h*eag* expression with antisense oligodeoxynucleotides (ODNs) should decrease the proliferation rate in these tumor cells. Therefore, a 19-mer antisense phosphorothioate ODN (5'-CAGCCATGGTCATCCTCCC) (SEQ ID NO: 15) spanning the putative initiation codon of h*eag* was used to test inhibition of proliferation. The sense ODN and a scrambled sequence (gtcggtaccagtaggaggg) (SEQ ID NO: 16) were used as controls. Data shown in Figure 16A confirms the efficiency of the antisense ODN treatment in reducing the h*eag* mRNA content in EFM cells. A reduction in heag mediated K^+ currents in SHSY-5Y cells by treatment with antisense ODN is shown in Fig. 16B and C.

IN THE CLAIMS

1. (Twice Amended) A nucleic acid molecule comprising a nucleic acid sequence encoding a (poly)peptide having a function of the human K^+ ion *eag* channel, wherein the nucleic acid sequence is selected from the group consisting of:

(a) a nucleic acid sequence comprising a nucleic acid molecule encoding the polypeptide having the amino acid sequence SEQ ID NO:3 or SEQ ID NO:4;

(b) the nucleic acid sequence SEQ ID NO:13 or SEQ ID NO:14;

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(c) a nucleic acid sequence that hybridizes to the complementary strand of a nucleic acid molecule of (a) or (b) at 4XSSC at 65°C or at 4XSSC at 42°C in 50% formamide; and

(d) a nucleic acid molecule being degenerate to the sequence of the nucleic acid molecule of (c).

3. (Twice Amended) The nucleic acid molecule of claim 1 [or 2], wherein the nucleic acid molecule is DNA.

4. (Twice Amended) The nucleic acid molecule of claim 1 [or 2], wherein the nucleic acid molecule is RNA.

5. (Twice Amended) The nucleic acid molecule of claim 1 [or claim 2], wherein the nucleic acid sequence encodes a fusion protein.

6. (Twice Amended) A vector comprising the nucleic acid molecule of claim 1 [or claim 2].

8. (Twice Amended) A host cell transformed with the vector of claim 6.

9. (Twice Amended) The host cell of claim 8, wherein the [host] cell is selected from the group consisting of a mammalian cell, a fungal cell, a plant cell, an insect cell and a bacterial cell.

14. (Twice Amended) A composition comprising the nucleic acid molecule of claim 1 [or claim 2], a vector comprising said nucleic acid molecule, a polypeptide encoded by said nucleic acid molecule, [and/or the] an antibody specifically directed against

said polypeptide, or optionally, in further combination with any one of the nucleic acid molecule, the vector, the polypeptide or the antibody, wherein the composition additionally comprises a pharmaceutically acceptable carrier [and/or diluent and/or excipient].

15. (Twice Amended) A diagnostic composition comprising the nucleic acid molecule of claim 1 [or claim 2], a vector comprising said nucleic acid molecule, a polypeptide encoded by said nucleic acid molecule [and/or] or an antibody specifically directed against said polypeptide.

32. (Twice Amended) A kit comprising the nucleic acid molecule of claim [2] 1, a vector comprising the nucleic acid molecule, [the polypeptide of claim 11 and/or] a polypeptide encoded by the nucleic acid molecule or [the] an antibody [of claim 12 or 13] specifically directed against said polypeptide.